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Serial No. 09/853,859

AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

IN THE SPECIFICATION

The Examiner objects to an alleged informality in the specification. On page 15, the example is labeled as "Example 1." The Examiner states that label has already been used. Applicants respectfully point out that the earlier label used on page 9 is for "Preparation 1." As such, "Example 1" is used on page 15 of the specification for the first time and is, thus, not in need of correction.

IN THE CLAIMS

Please amend claim 12 as follows:

B'

12. (Amended) The method according to Claim 11, wherein the patient is administered 5 μg/kg/hr to about 30 μg/kg/hr of human activated protein C.

REMARKS

Heparin is administered parenterally in vascular surgery and in the treatment of postoperative thrombosis and embolism. Approximately 1% to 30% (average: 5%) of patients receiving heparin have an immunologic reaction resulting in heparin-induced thrombocytopenia (HIT). These adverse events may develop into heparin-induced thrombocytopenia and thrombosis syndrome (HITTS). Patients with HITTS are at a substantial risk for debilitating or life-threatening venous or arterial thrombosis such as lower limb swelling or ischemia, stroke, or myocardial infarction - with a reported combined mortality and major morbidity of 25% to 37%. Thus, HIT is one of the most

important drug-induced thrombocytopenic disorders that a physician must manage. Its importance is evident for several reasons, including, the high prevalence of heparin usage; the high frequency of thrombocytopenia; the lack of a better alternative anti-thrombotic agent; and the concomitant occurrence of thrombotic complications.

Currently, treatment of HIT includes discontinuation of heparin and administration of alternative anti-thrombotic therapy. However, discontinuing heparin leaves the patients with thrombo-emboli or at high risk of thromboembolism without means for anticoagulation. Plus, using anticoagulants other than heparin can cause an adverse reaction with heparin-specific antibodies, take several days to take effect, or even be linked to venous limb gangrene. Hence, an effective treatment for HIT is needed. Applicants' invention is the first to describe a treatment of HIT with protein C, human protein C zymogen, or human activated protein C.

Claims 11 through 17 are pending in this case. Claim 12 has been amended to change the dependency so the claim properly depends on Claim 11. Basis for this amendment may be found in the specification, for example at p. 8, lines 13 through 15. Applicants assert that no new matter has been added by way of the amendment. Entry of the above amendment is requested. Attached hereto is a marked-up version of the changes made to the claim by the current amendment. The attached page is captioned "Version with markings to show changes made."

Serial No. 09/853,859

REJECTION OF CLAIMS 11-17 UNDER 35 U.S.C § 112, FIRST PARAGRAPH

Claims 11 through 17 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully assert that the invention is fully enabled and request withdrawal of this rejection.

According to MPEP 2164.04, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention (*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The Examiner initially asserts lack of enablement due to the specification having "no working examples demonstrating that this therapy actually works as claimed." The Examiner also points to Example 4 (labeled as Example 1 in the specification) as lacking results and being prophetic. Applicants agree with the Examiner that Example 4 is indeed prophetic. However, Applicants also respectfully point out that under MPEP 2164.02, compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." According to *Gould v. Quigg*, "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987). Applicants describe in Example 4 that treatment of HIT includes preventing the thrombotic sequelae of the syndrome by administering r-aPC,

an inhibitor of thrombin synthesis. Additionally, the example teaches a particular dosage and duration for r-aPC administration - 48 μg/kg/hr for 96 hours - within the range disclosed by the specification and used for the treatment of HIT. This dosage has been shown in previous human trials to raise the activated partial thromboplastin time (APTT) clotting assay result to two times the baseline level. These disclosures enable a person of ordinary skill in the art to treat a patient suffering from HIT with r-aPC at the proper dosage level and for the appropriate duration. Furthermore, a prophetic example does not inhibit enablement. As such, Applicants respectfully request withdrawal of this rejection.

The Examiner further indicates that the application allegedly lacks enablement since the ordinary person skilled in the art would not be reasonably apprised of when and how to safely administer aPC to treat HIT. The Examiner states that the claims lack enablement due to the absence of a working example in view of Gardyn et al. (1995). Gardyn involves an aPC resistant patient that died of HIT. According to the Examiner, the skilled artisan would not administer aPC to an aPC resistant person affected by HIT. This point appears to be due to the Examiner's interpretation of Gardyn's teaching. However, Gardyn does not teach anything about how to treat aPC resistant persons as compared to persons without aPC resistance. Also, Gardyn supplies no teachings with respect to aPC treatment for HIT. Since aPC was not administered to the patient, Gardyn is not able to direct a person of ordinary skill in the art either toward or away from aPC administration to an aPC resistant person with HIT.

Additionally, the Examiner states that the data in Gardyn "suggest[s] that there might be a correlation between HIT and thrombosis in aPC resistant patients." Gardyn is merely the first reported case of thrombosis associated with HIT in a patient with aPC resistance. The paper stands as an observation of a single patient's condition. Respectfully, Gardyn does not establish any link between HIT induced thrombosis and aPC-resistance. The case in Gardyn "raises the question of whether there may be a link between APC resistance and the thrombotic process induced by HIT." Yet, Gardyn also points out that "[t]hrombosis induced by HIT is a rather rare condition and hence may not necessarily be linked to the congenital factor V-anomaly" (i.e. aPC resistance). At best, the work of Gardyn can be regarded as a call for a future study to determine the "frequency of APC resistance in patients with HIT and thrombosis [which would] tell us whether the two conditions are associated."

All of these points illustrate that Gardyn does not disclose teachings that would make the person of ordinary skill in the art question the administration of aPC to a patient suffering from HIT that is taught by Applicants, regardless of whether the patient is aPC resistant or not. Gardyn does not teach anything with respect to treating HIT with aPC nor does it disclose which persons can or cannot receive treatment of any sort, nevertheless aPC. Alternatively, Applicants have provided teachings that would enable a person of ordinary skill in the art to treat patients suffering from HIT with effective amounts of aPC.

Since aPC treatment and patient determination for such treatment is not addressed in Gardyn, the reference

has no effect upon Applicants' disclosure. As such, Applicants' disclosure provides the information needed to enable the claims. Applicants, thus, respectfully request withdrawal of the rejection.

REJECTION OF CLAIMS 12-13 UNDER 35 U.S.C § 112, SECOND PARAGRAPH

Claims 12 through 13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicants thank the Examiner for pointing out the typographical error in Claim 12. Claim 12 is now amended to properly depend from Claim 11. However, Claim 13 contains no errors, making any amendment unnecessary. In view of these points, Applicants respectfully request withdrawal of this rejection.

REJECTION OF CLAIMS 11-17 UNDER 35 U.S.C § 103(a)

Claims 11 through 17 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Drohan et al. (US 5,589,604) or Lubon et al. (US 5,831,141). Applicants respectfully assert that the Examiner has failed to set forth a *prima facie* case of obviousness and request withdrawal of this rejection.

In *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the court defined the test for determining obviousness under 35 U.S.C. § 103: 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. The USPTO bears the burden of establishing a *prima facie* case. (*In re*

Piasecki, 745 F.2d 1468 (Fed. Cir. 1984)). In order to establish a *prima facie* case, the Examiner must show 1) some suggestion or motivation to modify the reference or to combine reference teachings (*In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988)); 2) the proposed modification had a reasonable expectation of success by a skilled artisan at the time of the invention (*Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991)); and 3) the prior art reference or combination of references must teach or suggest all limitations of the claims (*In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness.

Applicants discovered an important, previously unknown method for treating patients suffering from HIT using protein C, human protein C zymogen, or human activated protein C. The Examiner correctly states that both Drohan and Lubon disclose HIT as a clinical situation for which protein C administration may be beneficial. Additionally, the Examiner correctly points out that Drohan and Lubon "lack specifying the effective amounts or administration means." As such, these references lack key elements taught by Applicants - the particularized aPC dose range and administration means critical for treating HIT. Without such teachings, both Drohan and Lubon fail to provide information that would render Applicants' invention obvious.

The Examiner further states that the skilled artisan would have been motivated to administer aPC to treat HIT at effective dosages and regimens because the disclosure admits that "[t]hose skilled in the art can readily optimize pharmaceutically effective dosages and

administrative regimens for therapeutic compositions comprising protein C." However, this quote is taken in isolation from the rest of Applicants' disclosure. That specific sentence continues with the caveat "as determined by good medical practice and the clinical condition of the individual patient." Furthermore, the disclosure directly following that sentence provides particularized dosage and administration information to the skilled artisan. Taken in context, dosage and administration optimization for each patient's individual needs is available within the dosage ranges and administration options taught by Applicants. Applicants also note that one definition for the word 'optimize' is "to make as perfect or effective as possible" (The American Heritage® Dictionary of the English Language, Fourth Edition). Using good medical practice to focus Applicants' aPC teachings for each individual patient allows for the most perfect or effective HIT treatment possible. Unlike the current application, the teachings of Drohan and Lubon - that patients with HIT may benefit from protein C - without more are useless for any clinical application. Alternatively, Applicants provide the very details necessary to treat a patient suffering from HIT. Therefore, Applicants' invention is not obvious from Drohan or Lubon.

Additionally, no evidence exists to indicate that the skilled artisan would have been motivated to modify Drohan or Lubon in order to achieve Applicants' invention. Beyond the limited disclosure on the potential benefits of protein C for addressing HIT, these references specifically teach protein C production via a transgenic animal that secretes protein C into its milk. Indeed, neither reference provides the skilled artisan with any direction or

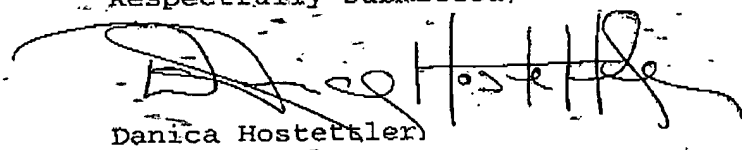
suggestions on what parameters to address or how to proceed to provide safe and effective HIT treatment with protein C. In contrast, Applicants provide specific dosage and administration information for using aPC to treat HIT-afflicted patients. Given all of the noted points, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants assert that the above-stated remarks obviate the noted rejections. This invention is fully enabled, both alone and in view of Gardyn. Furthermore, the invention is not obvious from either Drohan or Lubon.

In view of these points, Applicants courteously solicit reconsideration of these rejections and passage of this case to issuance.

Respectfully submitted,



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February 25, 2003

Serial No. 09/853,859

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claim 12 has been amended as follows:

12. (Amended) The method according to Claim [1] 11 wherein the patient is administered 5 μg/kg/hr to about 30 μg/kg/hr of human activated protein C.

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